

**Supplemental Table 1. Pharmacokinetic Terms [15, 20, 24, 122]**

<b>Maximum concentration (<math>C_{max}</math>)</b>	The maximum or “peak” concentration of the drug observed during a dosing interval [15, 24]
<b>Minimum concentration (<math>C_{min}</math>)</b>	The minimum or “trough” concentration of the drug observed after its administration and just prior to the absorption of a subsequent dose [24]
<b>Time to maximum concentration (<math>t_{max}</math>)</b>	The time after administration of the drug when the maximum plasma concentration ( $C_{max}$ ) is reached [15]
<b>Elimination half-life (<math>t_{1/2}</math>)</b>	The time required for 50% of the drug to be eliminated [15, 24]
<b>Apparent half-life (<math>t_{1/2}</math>)</b>	For controlled-release preparations, the rate of decline of the drug’s plasma concentration is due to the slowest rate constant. In the case of an LAI this is the absorption rate. In such conditions, the observed <b>half-life</b> is called <b>apparent half-life</b>
<b>Bioavailability (F)</b>	The extent, expressed as a fraction or percentage, of the administered drug dose that enters the systemic circulation compared to IV administration. $F=AUC/AUC_{IV}$ [15, 20]
<b>Area under the curve (AUC)</b>	The area under the concentration-time curve (the integral), which is the total exposure to the drug [15, 20]
<b>Steady state</b>	The condition that is attained when the amount of drug administered is equivalent to the amount of drug eliminated within any dosing interval (usually considered to be after 4–5 half-lives) [15, 20, 24, 122]
<b>Volume of distribution (<math>V_d</math>)</b>	The extent of distribution of a drug from the plasma to the tissues or the apparent volume in the body which contains the compound  (in one-compartment model, $V_d=F\times Dose/Concentration\ in\ plasma$ ) [15, 20]

LAI long-acting injectable, IV intravenous.

**Supplemental Table 2. Summaries of Studies Included in the Literature Analysis<sup>a</sup>**

**Flupentixol**

References	Study design	N	Age (years)	Setting	Duration	LAI antipsychotic	Comparator	Assessments	Outcomes	Flupentixol:
Jorgensen et al 1982 [44]	3-phase, PK study	9	Range: 25–62	3 sites: Denmark Sweden	20–32 weeks	(1) Flupentixol 1 decanoate	(2) Oral flupentixol (3) IV flupentixol	Radioimmunoassay: Plasma concentrations	<i>Flupentixol decanoate:</i> t <sub>max</sub> : 2–14 days t <sub>1/2</sub> : 46 days C <sub>max</sub> /C <sub>min</sub> : 2.4 AUC: 28.8 ng h/mL	<i>Oral flupentixol:</i> t <sub>max</sub> : 4 hours t <sub>1/2</sub> : 33.9–35.9 hours C <sub>max</sub> /C <sub>min</sub> : 2.2 AUC: 23.6–24.8 ng h/mL

**Fluphenazine**

References	Study design	N	Age (years)	Setting	Duration	LAI antipsychotic	Comparator	Assessments	Outcomes	Fluphenazine:
Cohen et al 1985 [123]	PK study	76	—	1 site	7+ years	(1) Fluphenazine decanoate	N/A	Radioreceptor assay: Plasma concentration-dose correlation	<i>Fluphenazine decanoate:</i> 12.5 mg decanoate to 4.2 nM fluphenazine eq. 25 mg enanthate to 6.5 nM fluphenazine eq. 37.5 mg enanthate to 10 nM fluphenazine eq. 50 mg enanthate to 13 nM fluphenazine eq.	<i>Fluphenazine enanthate:</i> 12.5 mg enanthate to 3.1 nM fluphenazine eq. 25 mg enanthate to 4.8 nM fluphenazine eq. 37.5 mg enanthate to 6 nM fluphenazine eq. 50 mg enanthate to 7.5 nM fluphenazine eq. 75 mg enanthate to 10 nM fluphenazine eq.
Dencker et al 1988 [48]	3-phase, single-dose, PK study	6	Range: 27–59	—	7.5 months – 2+ years	(1) Fluphenazine heptanoate 250 mg/wk	(2) Single-dose oral fluphenazine 400 mg	Assay: Plasma concentrations	<i>IM fluphenazine heptanoate 250 mg:</i> C <sub>ss</sub> : 3–6 µg/L	<i>Single-dose oral fluphenazine 200–500 mg:</i> C <sub>ss</sub> : 25–150 µg/L 400 mg: C <sub>max</sub> : 27–126 µg/L t <sub>max</sub> : 2–4 hours t <sub>1/2</sub> : 3.4–43.6 hours AUC: 667–1310 µg h/L

<b>Heresco-Levy et al 1997 [124]</b>	2-phase, maintenance dose-reduction study	41	Mean: 39.6– 41.6	1 site	26 months	(1) Fluphenazine decanoate 10 mg/4 wk  (2) Fluphenazine decanoate 35 mg/4 wk	N/A	<i>Radioreceptor assay:</i> Plasma concentration-dose correlation	<i>Fluphenazine decanoate 10 mg/4 wk:</i> Mean serum neuroleptic levels: Baseline: 248.4 ng/mL Week 4: 230.2 ng/mL Week 56: 78.9 ng/mL	<i>Fluphenazine decanoate 35 mg/4 wk:</i> Mean serum neuroleptic levels: Baseline: 288.8 ng/mL Week 4: 325.8 ng/mL Week 56: 270.9 ng/mL
<b>Soni et al 1988 [51]</b>	PK study	4–6	Range: 18–60	—	—	(1) Fluphenazine decanoate	N/A	<i>Radioimmunoassay:</i> Plasma concentrations	<i>Fluphenazine decanoate:</i> <i>Site of injection:</i> No significant differences in plasma profiles when injected into buttock vs thigh  <i>Massage of injection site:</i> Significantly lower serum fluphenazine concentrations after massage vs without massage at 0.5 and 1-hour postinjection  <i>Muscle activity:</i> Decrease in mean serum concentration after seventh day postinjection; no differences observed on day of injection	

### Haloperidol

References	Study design	N	Age (years)	Setting	Duration	LAI antipsychotic	Comparator	Assessments	Outcomes	
<b>Deberdt et al 1980 [38]</b>	Prospective study	37	Median: 48	—	3–12 months	(1) Haloperidol decanoate, 10-, 20-, or 30-fold of oral haloperido l dose q4w	N/A	<i>Radioimmunoassay:</i> Plasma concentrations	<i>Haloperidol decanoate:</i> Mean concentrations (all plasma samples, except those of the first 3 days): 0.8–3.2 ng/mL Mean concentrations (after second injection): 2–8 ng/mL C <sub>ss</sub> achieved after third injection	
<b>Eyles et al 1992 [125]</b>	PK study	10	—	—	—	(1) Haloperidol decanoate, 25–400 mg/4 wk	N/A	<i>Radioreceptor assay:</i> Plasma and blood concentrations	<i>Haloperidol decanoate:</i> Plasma and blood concentrations of haloperidol were not significantly different	

Panagiotidis et al 2007 [58]	PK study	26	Range: 28–83	Sweden	—	(1) Haloperidol decanoate, 0.4–14.3 mg/d	N/A	HPLC: Plasma concentrations	<u>Haloperidol decanoate:</u> C <sub>ss,peak</sub> : 1.6–67 nmol/L C <sub>ss,trough</sub> : 1.0–49 nmol/L
Reyntjens et al 1982 [39]	Follow-up, PK study	181	—	—	24 months	(1) Haloperidol decanoate, 20–400 mg/4 wk	N/A	Radioimmunoassay: Plasma concentration-dose correlation	<u>Haloperidol decanoate (100 mg):</u> C <sub>ss,min</sub> : 4 ng/mL C <sub>ss,max</sub> : 8 ng/mL C <sub>ss</sub> achieved after third monthly injection
Wei et al 1996 [57]	Prospective study	21	Mean: 39.3	Taiwan	20 weeks	(1) Haloperidol decanoate, 100 mg/wk (loading dose), 100 mg/2 wk, and 100 mg/4 wk	(2) Oral haloperidol, 10 or 20 mg	HPLC: Plasma concentrations	<u>Haloperidol decanoate:</u> <u>Oral haloperidol 10 mg (weeks 1–4):</u> Mean concentration: 3.61–7.58 ng/mL <u>Oral haloperidol 20 mg (weeks 1–4):</u> Mean concentration: 3.37–6.63 ng/mL <u>Oral haloperidol 10 mg (weeks 4–6):</u> Mean concentration: 7.54–8.06 ng/mL <u>Oral haloperidol 20 mg (weeks 4–6):</u> Mean concentration: 14.53–17.31 ng/mL

### Zuclopentixol

References	Study design	N	Age (years)	Setting	Duration	LAI antipsychotic	Comparator	Assessments	Outcomes	
Viala et al 1988 [60]	Comparative PK study	17	Range: 23–60	—	24 weeks	(1) Zuclopentixol decanoate, 200–1200 mg/3 wk  (2) Fluphenazine decanoate, 50–100 mg/3 wk	N/A	HPLC: Plasma concentrations	<u>Zuclopentixol 200–1200 mg:</u> C <sub>max</sub> : 5.6–36.0 ng/mL <u>Fourth dosage period:</u> Max C <sub>max</sub> /C <sub>min</sub> : 7.50 Min C <sub>max</sub> /C <sub>min</sub> : 1.58 Mean C <sub>max</sub> /C <sub>min</sub> : 3.95  <u>Eighth dosage period:</u> Max C <sub>max</sub> /C <sub>min</sub> : 4.48 Min C <sub>max</sub> /C <sub>min</sub> : 1.70 Mean C <sub>max</sub> /C <sub>min</sub> : 2.80	<u>Fluphenazine 50–100 mg:</u> C <sub>max</sub> : 1.1–4.8 ng/mL <u>4<sup>th</sup> dosage period:</u> Max C <sub>max</sub> /C <sub>min</sub> : 8.20 Min C <sub>max</sub> /C <sub>min</sub> : 1.38 Mean C <sub>max</sub> /C <sub>min</sub> : 3.24  <u>Eighth dosage period:</u> Max C <sub>max</sub> /C <sub>min</sub> : 2.75 Min C <sub>max</sub> /C <sub>min</sub> : 1.38 Mean C <sub>max</sub> /C <sub>min</sub> : 2.10

### Aripiprazole

References	Study design	N	Age (years)	Setting	Duration	LAI antipsychotic	Comparator	Assessments	Outcomes
Salzman et al 2017 [40]	PK modeling study (10 studies)	1266	Mean: ~40–47	—	—	(1) AM, 400 mg  (2) AL, 441 mg/4 wk  (3) 882 mg/4 wk	Oral aripiprazole	PopPK modeling and simulations: Plasma concentrations	<u>AM 400 mg:</u> C <sub>avg,ss</sub> : 269 ng/mL (deltoid) C <sub>avg,ss</sub> : 291 ng/mL (gluteal) C <sub>min,ss</sub> : ~200 ng/mL  <u>AL 441 mg:</u> C <sub>avg,ss</sub> : 117 ng/mL  <u>882 mg:</u> C <sub>avg,ss</sub> : 225 ng/mL C <sub>min,ss</sub> : ~175 ng/mL
Raoufinia et al 2017 [62]	2 (single-dose and multiple-dose), phase 1, open-label, randomized, parallel-arm studies	Single-dose study: 37  Multi-dose study: 141	Mean: 43.9–44.5	17 sites: USA	—	(1) Aripiprazole LAI, 400 mg/4 wk in deltoid muscle  (2) Aripiprazole LAI, 400 mg/4 wk in gluteal muscle	N/A	Noncompartmental methods: Plasma concentrations	<u>Single-dose study:</u> Deltoid (first injection): C <sub>max</sub> : 170 ng/mL t <sub>max</sub> : 7.1 days AUC <sub>t</sub> : 7,360 ng d/mL AUC <sub>∞</sub> : 7,590 ng d/mL t <sub>1/2</sub> : 17.8 days  <u>Multiple-dose study:</u> Deltoid/deltoid (1 <sup>st</sup> injection): C <sub>max</sub> : 135 ng/mL t <sub>max</sub> : 14.3 days  <u>Gluteal/deltoid (first injection):</u> C <sub>max</sub> : 126 ng/mL t <sub>max</sub> : 13.9 days  <u>Combined deltoid/deltoid and gluteal/deltoid groups (fifth injection):</u> C <sub>max,ss</sub> : 328 ng/mL C <sub>min,ss</sub> : 239 ng/mL AUC <sub>t</sub> : 7027 ng d/mL t <sub>max</sub> : 3.95 days
Hard et al 2017 [66]	Phase 1, open-label, PK study	104	Mean: 44.5	15 sites: USA	44 weeks	(1) AL, 441 mg/4 wk  (2) AL, 882 mg/6 wk  (3) AL, 1064 mg/8 wk	N/A	Noncompartmental methods: Plasma concentrations	t <sub>max</sub> : 24.4–35.2 days  <u>AL 441 mg:</u> C <sub>max</sub> : 161 ng/mL C <sub>avg,ss</sub> : 125.8 ng/mL AUC <sub>t</sub> : 3520 ng d/mL t <sub>1/2</sub> : 57.2 days  <u>AL 882 mg:</u> C <sub>avg,ss</sub> : 131.1 ng/mL AUC <sub>t</sub> : 7880 ng d/mL t <sub>1/2</sub> : 53.9 days  <u>AL 1064 mg:</u> AUC <sub>t</sub> : 5510 ng d/mL t <sub>1/2</sub> : 55.1 days
Hard et al 2017 [63]	Population PK modeling (5 trials)	616	Median: 39–47	—	—	(1) AL, 441 mg/4 wk  (2) AL, 662 mg/4 wk	N/A	HPLC (LC/MS/MS); PK modeling: Plasma concentrations	<u>AL 441 mg/4 wk:</u> C <sub>min,ss</sub> : 166 ng/mL C <sub>min,ss</sub> : 112 ng/mL  <u>AL 662 mg/4 wk:</u> C <sub>max,ss</sub> : 184 ng/mL C <sub>avg,ss</sub> : 178 ng/mL  <u>AL 882 mg/4 wk:</u> C <sub>min,ss</sub> : 219 ng/mL  <u>AL 882 mg/6wk:</u> C <sub>min,ss</sub> : 128 ng/mL C <sub>max,ss</sub> : 168 ng/mL C <sub>avg,ss</sub> : 150 ng/mL

							C <sub>max,ss</sub> : 122 ng/mL	C <sub>max,ss</sub> : 234 ng/mL
					(3) AL, 882 mg/4 wk		C <sub>avg,ss</sub> : 117 ng/mL	C <sub>avg,ss</sub> : 225 ng/mL
					(4) AL, 882 mg/ 6 wk			
<b>Hard et al 2018 [68]</b>	Phase 1, randomized, double-blind, placebo- controlled study	161 Mean: 44	13 sites: USA	6 months	(1) 1-day AL <sub>NCD</sub> initiation regimen + 30 mg oral aripiprazole (day 1) + AL 441 mg	N/A	LC/MS/MC: Plasma concentrations	<i>1-day AL<sub>NCD</sub></i> <i>initiation</i> <i>regimen +</i> <i>AL 441 mg:</i> AUC <sub>0-28</sub> : 3570.7 ng d/mL
					(2) 1-day AL <sub>NCD</sub> initiation regimen + 30 mg oral aripiprazole (day 1) + AL 882 mg			4256.4 ng d/mL
					(3) 21-day oral aripiprazole 15 mg initiation regimen + AL 441 mg			AUC <sub>0-28</sub> : 441 mg:
					(4) 21-day oral aripiprazole 15 mg initiation regimen + AL 882 mg			3371.6 ng d/mL
<b>Hard et al 2018 [126]</b>	Population PK modeling (4 trials)	343 Mean: 45.2	—	—	(1) AL, 441 mg/ 4 wk	N/A	PopPK modeling and simulations: No late dose: Population parameter estimates	<i>AL</i> <i>441 mg/4 wk:</i> <i>662 mg/4 wk:</i> <i>882 mg/4 wk:</i> C <sub>max</sub> : 153.0 C <sub>max</sub> : ng/mL
					(2) AL, 662 mg/ 4 wk			227.1 ng/mL
					(3) AL, 882 mg/ 4 wk			Late dose and recovery: and recovery: C <sub>max</sub> :
					(4) AL, 882 mg/ 6 wk			218.8 ng/mL
					(5) AL, 1062 mg/ 8 wk			286.5 ng/mL
								Late dose and recovery : C <sub>max</sub> :
								226.4 ng/mL
								C <sub>max</sub> : 211.6 ng/mL

<b>Risinger et al 2017</b> <i>[127]</i>	Phase 1, randomized, open-label, parallel study	139	Mean: 44.8–46.3	16 sites: USA	24 weeks	(1) AL, 1064 mg/8 wk  (2) AL, 882 mg/6 wk  (3) AL, 441 mg/4 wk	N/A	<i>Noncompartmental methods:</i> PK parameters	t <sub>max</sub> : 20–34 days  <u>AL 1064 mg/8 wk</u>  C <sub>max</sub> : 188.8 ng/mL C <sub>avg</sub> : 140.7 ng/mL AUC <sub>T</sub> : 7880.0 ng d/mL t <sub>1/2</sub> : 53.9 days	<u>AL 882 mg/6 wk</u>  C <sub>max</sub> : 171.6 ng/mL C <sub>avg</sub> : 131.1 ng/mL AUC <sub>T</sub> : 5505.1 ng day/mL t <sub>1/2</sub> : 55.1 days	<u>AL 441 mg/4 wk</u>  C <sub>max</sub> : 161.2 ng/mL C <sub>avg</sub> : 125.8 ng/mL AUC <sub>T</sub> : 3522.4 ng d/mL t <sub>1/2</sub> : 57.2 days
<b>Turncliff et al 2014</b> <i>[121]</i>	Phase 1, multicenter, randomized, open-label, single-dose study	46	Mean: 42.5	4 sites: USA	117 days	(1) AL, 441 mg in deltoid muscle  (2) AL, 441 mg in gluteal muscle	N/A	<i>Noncompartmental methods:</i> plasma concentrations	t <sub>1/2</sub> : 15.4–19.2 days  <u>AL 441 mg in deltoid muscle:</u>  <u>Aripiprazole:</u> C <sub>max</sub> : 57.4 ng/mL t <sub>max</sub> : 44.1 days AUC <sub>last</sub> : 2744 ng d/mL AUC <sub>0→∞</sub> : 3351 ng d/mL	<u>AL 441 mg in gluteal muscle:</u>  <u>Aripiprazole:</u> C <sub>max</sub> : 46.8 ng/mL t <sub>max</sub> : 50.0 days AUC <sub>last</sub> : 2275 ng d/mL AUC <sub>0→∞</sub> : 3598 ng d/mL	
<b>Weiden et al 2020</b> <i>[128]</i>	Phase 1, open-label, multicenter study	104	Mean: 44.3	15 sites: USA	44 weeks	(1) AL, 1064 mg q8wk  (2) AL, 882 mg q6wk  (3) AL, 441 mg q4wk	N/A	<i>Noncompartmental methods:</i> Plasma concentrations	AL, 1064 mg q8wk t <sub>1/2</sub> : 53.9 days C <sub>max</sub> (first, last dose): 129.6, 188.8 ng/mL Median t <sub>max</sub> (first, last dose): 43.4, 34.4 days AUC <sub>last</sub> (first, last dose): 3692.4, 14,188.1 ng d/mL AUC <sub>c</sub> (first, last dose): 3945.0, 7880.0 ng d/mL	AL, 441 mg q4wk t <sub>1/2</sub> : 57.2 days C <sub>max</sub> (first, last dose): 33.0, 161.2 ng/mL Median t <sub>max</sub> (first, last dose): 27.9, 28.0 days AUC <sub>last</sub> (first, last dose): 368.64, 11,451.4 ng d/mL AUC <sub>c</sub> (first, last dose): 363.5, 3522.4 ng d/mL	

<b>Hard et al 2019 [129]</b>	Phase 1, randomized, open-label study	47	Mean: 48.6	—	~4 months	(1) AL, 441 mg in gluteal muscle  (2) AL, 662 mg in gluteal muscle  (3) AL, 882 mg in gluteal muscle  (4) AL, 1064 mg in gluteal muscle  (5) AL, 882 mg in deltoid muscle	N/A	Noncompartimental methods: Plasma concentrations	<u>AL in deltoid muscle:</u> $t_{1/2}$ : 14.9 days $C_{max}$ : 196.1 ng/mL Median $t_{max}$ : 17.0 days $AUC_{last}$ : 6419.0 ng d/mL $AUC_{0-\infty}$ : 6590.8 ng d/mL  <u>AL in gluteal muscle:</u> $t_{1/2}$ : 15.2 days $C_{max}$ : 175.0 ng/mL Median $t_{max}$ : 25.5 days $AUC_{last}$ : 6070.2 ng d/mL $AUC_{0-\infty}$ : 6437.2 ng d/mL
<b>Olanzapine</b>									
References	Study design	N	Age (years)	Setting	Duratio n	LAI antipsychotic	Comparator	Assessments	Outcomes
<b>Detke et al 2011 [73]</b>	PK modeling study (1 trial)	1065	Mean: 39	112 sites, 26 countries	24 weeks	(1) Olanzapine LAI, 45 mg/4 wk  (2) Olanzapine LAI, 150 mg/2 wk  (3) Olanzapine LAI, 405 mg/4 wk  (4) Olanzapine LAI, 300 mg/2 wk	(5) Oral olanzapine, 10, 15, or 20 mg/day	<i>PopPK modeling and simulations:</i> Plasma concentrations	Starting dose of 150 mg/2 wk or 300 mg/4 wk provides lower olanzapine concentrations during the first 8 weeks when given without a loading dose  Loading dose of 300 mg/2 wk exceeds target maintenance concentration start at week 4
<b>Heres et al 2014 [70]</b>	Population PK modeling study (5 trials)	1151	Range: 18–76	—	—	(1) Olanzapine LAI single dose (10–450 mg) and multiple doses (45–405 every 2, 3, or 4 weeks)	(2) Oral olanzapine, 5–20 mg/d	HPLC; noncompartmental methods: Population parameter estimates	<i>Olanzapine LAI 300 mg/2 wk:</i> $k_a$ : 0.000963 h <sup>-1</sup> $k_{el}$ : 0.0231 h <sup>-1</sup> Absorption $t_{1/2}$ : ~30 days $C_{max}$ : ~9.5 ng/mL $t_{max}$ : ~6 days Css achieved after ~12 weeks  <i>Oral olanzapine 20 mg/d:</i> $C_{max}$ : ~14 ng/mL $t_{max}$ : 10 hours
<b>Mitchell et al 2013 [71]</b>	Phase 1b, open-label, multicenter, nonrandomized, single- and multiple-dose, exploratory study	281	Mean: 39	18 sites: Belgium, Croatia, Spain, USA	3–6 months	(1) Olanzapine, Single dose 50–450 mg  (2) Olanzapine, 210, 255, 300, 405 mg/4 wk	N/A	HPLC: Plasma concentrations	<i>2-week injection interval:</i> <i>Olanzapine LAI 100 mg:</i> $C_{max,ss}$ : 13.5 ng/mL $t_{max,ss}$ : 96.0 hours $AUC_{t,ss}$ : 3530 ng h/mL $t_{1/2}$ : 322 hours $CL_{ss/F}$ : 28.4 L/F $C_{mean,ss}$ : 10.5 ng/mL  <i>4-week injection interval:</i> <i>Olanzapine LAI 210 mg:</i> $C_{max,ss}$ : 22.8 ng/mL $t_{max,ss}$ : 48 hours $AUC_{t,ss}$ : 9150 ng h/mL $t_{1/2}$ : 553 hours $CL_{ss/F}$ : 21.9 L/h $C_{mean,ss}$ : 13.6 ng/mL

<b>Tveito et al 2019 [130]</b>	Retrospective study	2791	Media n: 39,5 (LAI), 45 (Oral)	— years	~12.5 years	(1) Olanzapine LAI  (2) Olanzapine Oral	N/A	<i>Liquid chromatograph y-mass spectrometry: Serum concentrations</i>	<i>Olanzapine LAI</i> Dose adjusted (ng/mL): -VPA user: 1.6 (1.2-1.9) -VPA nonuser: 1.7 (1.7-1.8)	<i>Olanzapine Oral</i> Concentration Dose adjusted Concentration (ng/mL): -VPA user: 2.2 (2.1-2.3) -VPA nonuser: 2.7 (2.6-2.7)

### Paliperidone

References	Study design	N	Age (years)	Setting	Duratio n	LAI antipsychotic	Comparator	Assessments	Outcomes
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<b>Cleton et al 2014 [76]</b>	Single-dose, open-label, parallel, randomized, dose-proportionality, parallel-group study	210	Mean: 37.4– 43.8	28 sites: Canada Israel Poland Romania Slovakia Sweden Spain USA	147 days	(1) PP1M, 39, 78, 156, and 234 mg in deltoid muscle (single dose)  (2) PP1M, 39, 78, 156, and 234 mg in gluteal muscle (single dose)	N/A	<i>Noncompartimental methods:</i> Plasma concentrations	<u>PP1M 39, 78, 156, and 234 mg deltoid:</u> $t_{max}$ : 13.0–14.0 days $C_{max}$ : 5.3–11.0 ng/mL $AUC_{last}$ : 9311–11,271 ng h/mL $AUC_{\infty}$ : 9574–10,266 ng h/mL $t_{1/2}$ : 24.9–43.7 days $CL/F$ : 4.4–5.4 L/h	<u>PP1M 39, 78, 156, and 234 mg</u> $t_{max}$ : 13.4–17.0 days $C_{max}$ : 5.1–8.7 ng/mL $AUC_{last}$ : 5966–9779 ng h/mL $AUC_{\infty}$ : 9652–10,557 ng h/mL $t_{1/2}$ : 25.1–49.1 days $CL/F$ : 4.6–5.2 L/h
<b>Coppola et al 2012 [80]</b>	Phase 1, multicenter, open-label, multiple-dose study	212	Mean: 40.7	30 centers: Belgium Croatia Spain Republic of Korea Malaysia Poland Slovakia Thailand Taiwan USA	1 year	(1) PP, 234 mg in deltoid muscle (day 1), 234 mg in deltoid or gluteal muscle (day 8); PP1M, 234 mg in deltoid or gluteal muscle (days 36– 344)	N/A	<i>Liquid chromatograph y-mass spectrometry:</i> Plasma concentrations	<u>PP 234 mg:</u> <i>Second injection:</i> $C_{predose}$ : 21.3 ng/mL $C_{min}$ : 17.0 ng/mL $C_{max}$ : 50.5 ng/mL $t_{max}$ : 7.96 days $AUC_{t}$ : 23,325 h ng/mL $C_{avg}$ : 34.7 ng/mL FI: 92.7% <u>PP 234 mg:</u> <i>Eighth injection:</i> $C_{predose}$ : 28.4 ng/mL $C_{min}$ : 27.0 ng/mL $C_{max}$ : 50.5 ng/mL $t_{max}$ : 8.48 days $AUC_{t}$ : 26,831 h ng/mL $C_{avg}$ : 40.0 ng/mL FI: 55.0%  <u>PP1M:</u> $C_{predose}$ : 39.9 ng/mL $C_{min}$ : 35.1 ng/mL $C_{max}$ : 56.5 ng/mL $t_{max}$ : 7.00 days $AUC_{t}$ : 31,970 h ng/mL $C_{avg}$ : 47.8 ng/mL FI: 41.2%	

<b>Gomeni et al 2016 [131]</b>	PK modeling study (1 trial)	201	Mean: 37.4–43.8	28 sites: Canada, Israel, Romania, Slovakia, Sweden, Spain, USA	147 days	(1) PP1M, 39, 78, 156, and 234 mg in deltoid muscle(single dose)	N/A	<i>PopPK modeling:</i> Population parameter estimates	<i>PP1M:</i> td: 11.3 hours ss: 1.65 tdl: 21.6 hours ss1: 9.66 ff: 0.585% V: 268 L kel: 0.04 h <sup>-1</sup>
<b>Helland et al 2017 [79]</b>	Retrospective database analysis	185	Median: — 40	—	25 weeks	(1) Paliperidone depot 12.5-200 mg/4 wk	N/A	<i>Liquid chromatograph y-mass spectrometry:</i> Plasma concentration	<i>Paliperidone depot:</i> Mean daily dose: 3.60 mg (100 mg/q4w) Serum concentration: 51.0 nmol/L C/D ratio: 16.1
<b>Hough et al 2009 [114]</b>	Randomized, multicenter, crossover study	252	Mean: 43	34 centers: Belgium, Bulgaria, Czech Republic, Germany, Slovakia, Republic of USA	25 weeks	(1) PP1M 78 mg (2) PP1M 117 mg (3) PP1M 156 mg	N/A	<i>Liquid chromatograph y-mass spectrometry:</i> Plasma concentrations	<i>PP1M:</i> t <sub>max</sub> : ~7 days
<b>Rosseu et al 2015 [75]</b>	Multiple-dose, open-label, randomized, parallel-group, single-center study	49	Mean: 43	Croatia	6 months	(1) PP1M, 156 mg in deltoid muscle day 1, 8, 36, 64 (2) PP1M, 156 mg in gluteal muscle day 1, 8, 36, 64	N/A	<i>Liquid chromatograph y-mass spectrometry:</i> Plasma concentrations	<i>PP1M 156 mg deltoid:</i> Second injection: C <sub>max</sub> : 33.2 ng/mL t <sub>max</sub> : 10.0 days AUC $\tau$ : 15,132 ng h/mL C <sub>avg</sub> : 22.6 ng/mL FI: 93.2% <i>PP1M 156 mg gluteal:</i> Second injection: C <sub>max</sub> : 27.2 ng/mL t <sub>max</sub> : 10.0 days AUC $\tau$ : 12,838 ng h/mL C <sub>avg</sub> : 19.1 ng/mL FI: 93.7%
								<i>Fourth injection:</i>	<i>Fourth injection:</i>

							$C_{max}$ : 29.4 ng/mL $t_{max}$ : 5.0 days AUC $\tau$ : 14,103 ng h/mL $C_{avg}$ : 21.1 ng/mL FI: 75.9%	$C_{max}$ : 22.7 ng/mL $t_{max}$ : 6.5 days AUC $\tau$ : 11,928 ng h/mL $C_{avg}$ : 17.7 ng/mL FI: 58.5%			
Russu et al 2018 [74]	PK modeling study (20 trials)	2575	—	—	(1) PP1M, 39, 78, 156, and 234 mg q4w	(2) Oral risperidone, 1, 2, 3, 4, and 6 mg/d	<i>PopPK modeling and simulations:</i> Plasma concentrations	<u>Maintenance dose conversion:</u> Oral risperidone 1 mg to PP1M 39 mg Oral risperidone 2 mg to PP1M 78 mg Oral risperidone 3 mg to PP1M 117 mg Oral risperidone 4 mg to PP1M 156 mg Oral risperidone 6 mg to PP1M 234 mg			
Samtani et al 2009 [78]	PK modeling study (11 trials)	1795	Median: 42	—	(1) PP1M, 39–1234 mg (single and multiple doses)	N/A	<i>PopPK modeling:</i> Population parameter estimates	<u>PP1M:</u> CL/F: 4.95 L/h V: 391 L $k_a \times 10^3$ : 0.488 h <sup>-1</sup>			
Samtani et al 2012 [132]	PK modeling study	—	—	—	(1) PP, 117 mg/4 wk (2) Risperidone LAI, 37.5 mg/2 wk	(3) Oral paliperidone ER, 6 mg/d (4) Oral risperidone IR, 3 mg/d	<i>PK modeling and simulations:</i> Plasma concentrations	<u>PP:</u> Number of days until plasma concentration was <2 ng/mL: 136 days 1 week treatment discontinuation $C_{min,discontinuation}/C_{min,ss}$ : 90% 4 week treatment discontinuation $C_{min,discontinuation}/C_{min,ss}$ : 64%	<u>Risperidone LAI:</u> Number of days until plasma concentration was <2 ng/mL: 32.9 days 1 week treatment discontinuation $C_{min,discontinuation}/C_{min,ss}$ : 35% 4 week treatment discontinuation $C_{min,discontinuation}/C_{min,ss}$ : 33%	<u>Oral paliperidone ER:</u> Number of days until plasma concentration was <2 ng/mL: 5.4 days 1 week treatment discontinuation $C_{min,discontinuation}/C_{min,ss}$ : 11% 4 week treatment discontinuation $C_{min,discontinuation}/C_{min,ss}$ : 0%	<u>Oral risperidone IR:</u> Number of days until plasma concentration was <2 ng/mL: 1 week 4 week treatment discontinuation $C_{min,discontinuation}/C_{min,ss}$ : 2% 4 week treatment discontinuation $C_{min,discontinuation}/C_{min,ss}$ : 0%

<b>Si et al 2014 [133]</b>	Open-label, randomized, parallel group, multicenter study	48	Mean: 51–56	China	210 days	(1) PP1M 39 mg days 1 and 8  (2) PP1M 156 mg days 1 and 8  (3) PP1M 234 mg days 1 and 8	N/A	<i>Liquid chromato- graphy-mass spectrometry:</i> Plasma concentrations	<i>PP1M 39 mg:</i> C <sub>max</sub> : 12.4 ng/mL t <sub>max</sub> : 13.3 days AUC <sub>0–35</sub> : 231.4 ng day/mL AUC <sub>0–210</sub> : 612.7 ng days/mL AUC <sub>0–∞</sub> : 664.9 ng days/mL t <sub>1/2</sub> : 55.1 days CL/F: 45.9 L/day	<i>PP1M 156 mg:</i> C <sub>max</sub> : 43.9 ng/mL t <sub>max</sub> : 13.1 days AUC <sub>0–35</sub> : 862.6 ng day/mL AUC <sub>0–210</sub> : 2006.5 ng day/mL AUC <sub>0–∞</sub> : 2330.1 ng day/mL t <sub>1/2</sub> : 66.5 days CL/F: 47.3 L/day	<i>PP1M 234 mg:</i> C <sub>max</sub> : 45.8 ng/mL t <sub>max</sub> : 14.0 days AUC <sub>0–35</sub> : 938.3 ng day/mL AUC <sub>0–210</sub> : 2829.6 ng day/mL AUC <sub>0–∞</sub> : 3496.1 ng day/mL t <sub>1/2</sub> : 82.7 days CL/F: 50.0 L/day
<b>Magnusson et al 2017 [115]</b>	PK modeling study (2 trials)	651	Median: 38	—	—	(1) PP3M	N/A	<i>PopPK modeling:</i> Population parameter estimates	<i>PP3M:</i> CL: 3.84 L/h V: 1,960 L ka <sub>1max</sub> : 90.4 µg/h ka <sub>3max</sub> : 164 µg/h		
<b>Ravenstijn et al 2016 [82]</b>	Phase 1, multicenter, randomized, open- label, parallel-group, single-dose study	308	Mean: 41.4– 42.6	72 sites: Belgium Bulgaria Croatia Israel Malaysia República de Korea Slovakia South Africa Spain Taiwan USA	53–58 273, 468, 702, or 819 mg in deltoid muscle (2) PP3M, 117, 234, 468, 546, 702, or 819 mg in gluteal muscle	(1) PP3M, N/A	<i>Liquid chromato- graphy-mass spectrometry:</i> Plasma concentrations	<i>PP3M 273 mg:</i> C <sub>max</sub> : 21.2 ng/mL t <sub>max</sub> : 24.0 days AUC <sub>∞</sub> : 46,480 ng h/mL t <sub>1/2</sub> : 51.7 days  <i>PP3M 468 mg:</i> C <sub>max</sub> : 28.0 ng/mL t <sub>max</sub> : 34.0 days AUC <sub>∞</sub> : 77,925 ng h/mL t <sub>1/2</sub> : 73.5 days  <i>PP3M 702 mg:</i> C <sub>max</sub> : 40.1 ng/mL t <sub>max</sub> : 24.0 days AUC <sub>∞</sub> : 131,651 ng h/mL t <sub>1/2</sub> : 71.8 days  <i>PP3M 819 mg:</i> C <sub>max</sub> : 57.9 ng/mL t <sub>max</sub> : 24.5 days AUC <sub>∞</sub> : 128,969 ng h/mL	<i>Gluteal:</i> <i>PP3M 117 mg:</i> C <sub>max</sub> : 10.1 ng/mL t <sub>max</sub> : 29.0 days AUC <sub>∞</sub> : 22,214 ng h/mL t <sub>1/2</sub> : 44.9 days  <i>PP3M 234 mg:</i> C <sub>max</sub> : 8.3 ng/mL t <sub>max</sub> : 27.5 days AUC <sub>∞</sub> : 42,963 ng h/mL t <sub>1/2</sub> : 79.6 days  <i>PP3M 546 mg:</i> C <sub>max</sub> : 36.7 ng/mL t <sub>max</sub> : 31.0 days AUC <sub>∞</sub> : 102,894 ng h/mL t <sub>1/2</sub> : 77.4 days  <i>PP3M 702 mg:</i> C <sub>max</sub> : 35.0 ng/mL t <sub>max</sub> : 28.0 days AUC <sub>∞</sub> : 123,273 ng h/mL t <sub>1/2</sub> : 81.5 days		

							$t_{1/2}$ : 56.9 days		
<b>Samtani et al 2013 [134]</b>	PK modeling study (2 trials)	606	—	—	—	<i>First set of simulation s:</i> (1) PP1M, 234 mg day 1/ 156 mg day 8  (2) PP1M, 234 mg day 1/ 156 mg day 4  (3) PP1M, 234 mg day 1/ 156 mg day 12	N/A PK modeling and simulations: Plasma concentrations	<i>First set of simulations:</i> <u>PP 234 mg /156 mg day 1/day 8:</u> C <sub>max</sub> : 29.8 ng/mL <u>PP 234 mg /156 mg day 1/day 4:</u> C <sub>max</sub> : 31.2 ng/mL <u>PP 234 mg /156 mg day 1/day 12:</u> C <sub>max</sub> : 26.7 ng/mL	<i>Second set of simulations:</i> <u>PP 234 mg day 1 /234 mg day 8:</u> C <sub>max</sub> : 34.6 ng/mL <u>PP 234 mg day 1 /156 mg day 4:</u> C <sub>max</sub> : 31.2 ng/mL <u>PP 234 mg day 1 /156 mg day 12:</u> C <sub>max</sub> : 26.7 ng/mL
						<i>Second set of simulation s:</i> (4) PP1M, 234 mg day 1/ 156 mg day 8  (5) PP1M, 234 mg day 1/ 156 mg day 4		<u>PP 234 mg day 1 /156 mg day 8:</u> C <sub>max</sub> : 29.8 ng/mL	

		(6) PP1M, 234 mg day 1/ 156 mg day 8									
		(7) PP1M, 234 mg day 1/ 156 mg day 12									
<b>Risperidone</b>											
References	Study design	N	Age (years)	Setting	Duratio n	LAI antipsychotic	Comparator	Assessments	Outcomes		
Gefvert et al 2005 [88]	Open-label, non-randomized study	13	Range: 23–54	4 sites: Sweden	17 weeks	(1) Risperdal Consta, 25 mg/2 wk  (2) Risperdal Consta, 50 mg/2 wk  (2) Risperdal Consta, 75 mg/2 wk	N/A	Radioimmunoassay:  Plasma concentrations	$t_{1/2}$ : 4–6 days  <u>Risperdal Consta 25 mg/2 wk:</u> <u>Risperidone:</u> <u>Third injection</u> $C_{predose}$ : 2.3 ng/mL $C_{min}$ : 1.5 ng/mL $C_{max}$ : 5.2 ng/mL $C_{max}/C_{min}$ ratio: 3.4  <u>Fourth injection</u> $C_{predose}$ : 2.9 ng/mL $C_{min}$ : 2.2 ng/mL $C_{max}$ : 6.4 ng/mL $C_{max}/C_{min}$ ratio: 2.5  <u>Fifth injection</u> $C_{predose}$ : 2.8 ng/mL $C_{min}$ : 1.9 ng/mL $C_{max}$ : 4.7 ng/mL $C_{max}/C_{min}$ ratio: 3.4 $C_{ss,avg}$ : 3.2 ng/mL $AUC_{336h}$ : 1062 ng h/mL	<u>Risperdal Consta</u> <u>Risperidone:</u> <u>Third injection</u> $C_{predose}$ : 5.2 ng/mL $C_{min}$ : 4.9 ng/mL $C_{max}$ : 8.1 ng/mL $C_{max}/C_{min}$ ratio: 1.8  <u>Fourth injection</u> $C_{predose}$ : 4.9 ng/mL $C_{min}$ : 4.2 ng/mL $C_{max}$ : 9.2 ng/mL $C_{max}/C_{min}$ ratio: 1.8  <u>Fifth injection</u> $C_{predose}$ : 6.0 ng/mL $C_{min}$ : 5.6 ng/mL $C_{max}$ : 9.7 ng/mL $C_{max}/C_{min}$ ratio: 1.9 $C_{ss,avg}$ : 8.0 ng/mL $AUC_{336h}$ : 2689 ng h/mL	<u>Risperdal Consta</u> <u>Risperidone:</u> <u>Third injection</u> $C_{predose}$ : 7.5 ng/mL $C_{min}$ : 5.7 ng/mL $C_{max}$ : 11.2 ng/mL $C_{max}/C_{min}$ ratio: 2.0  <u>Risperidone:</u> <u>Third injection</u> $C_{predose}$ : 4.8 ng/mL $C_{min}$ : 2.8 ng/mL $C_{max}$ : 13.2 ng/mL $C_{max}/C_{min}$ ratio: 4.0

	C <sub>max</sub> : 9.2 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 3.4  <i>Fourth injection</i> C <sub>predose</sub> : 5.2 ng/mL C <sub>min</sub> : 4.6 ng/mL C <sub>max</sub> : 9.3 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.2  <i>Fifth injection</i> C <sub>predose</sub> : 5.4 ng/mL C <sub>min</sub> : 4.1 ng/mL C <sub>max</sub> : 14.4 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 3.6 C <sub>ss,avg</sub> : 7.6 ng/mL AUC <sub>336h</sub> : 2553 ng h/mL  <u>Risperidone plus 9-hydroxyrisperidone:</u> <i>Third injection</i> C <sub>predose</sub> : 3.8 ng/mL C <sub>min</sub> : 3.8 ng/mL C <sub>max</sub> : 13.0 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.8  <i>Fourth injection</i> C <sub>predose</sub> : 8.9 ng/mL C <sub>min</sub> : 8.1 ng/mL C <sub>max</sub> : 16.3 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.4  <i>Fifth injection</i> C <sub>predose</sub> : 8.1 ng/mL C <sub>min</sub> : 6.3 ng/mL C <sub>max</sub> : 18.2 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 3.0 C <sub>ss,avg</sub> : 10.8 ng/mL AUC <sub>336h</sub> : 3613 ng h/mL	C <sub>predose</sub> : 9.5 ng/mL C <sub>min</sub> : 6.8 ng/mL C <sub>max</sub> : 16.0 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.2  <i>Fourth injection</i> C <sub>predose</sub> : 13.7 ng/mL C <sub>min</sub> : 10.8 ng/mL C <sub>max</sub> : 18.0 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 1.5  <u>Risperidone plus 9-hydroxyrisperidone:</u> <i>Third injection</i> C <sub>predose</sub> : 12.9 ng/mL C <sub>min</sub> : 11.5 ng/mL C <sub>max</sub> : 24.3 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.1 C <sub>ss,avg</sub> : 19.0 ng/mL AUC <sub>336h</sub> : 6386 ng h/mL  <i>Fourth injection</i> C <sub>predose</sub> : 14.5 ng/mL C <sub>min</sub> : 14.5 ng/mL C <sub>max</sub> : 48.0 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.8 C <sub>min</sub> : 15.3 ng/mL C <sub>max</sub> : 26.3 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.0  <i>Fourth injection</i> C <sub>predose</sub> : 18.6 ng/mL C <sub>min</sub> : 15.0 ng/mL C <sub>max</sub> : 28.1 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 1.5 C <sub>ss,avg</sub> : 18.6 ng/mL AUC <sub>336h</sub> : 9074 ng h/mL  <i>Fifth injection</i> C <sub>predose</sub> : 14.8 ng/mL C <sub>min</sub> : 10.8 ng/mL C <sub>max</sub> : 50.9 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 7.0 C <sub>min</sub> : 18.5 ng/mL C <sub>max</sub> : 33.6 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 1.9 C <sub>ss,avg</sub> : 27.0 ng/mL AUC <sub>336h</sub> : 9820 ng h/mL	C <sub>max</sub> : 34.9 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.5  <i>Fourth injection</i> C <sub>predose</sub> : 19.1 ng/mL C <sub>min</sub> : 10.7 ng/mL C <sub>max</sub> : 27.4 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 1.7  <i>Fifth injection</i> C <sub>predose</sub> : 10.7 ng/mL C <sub>min</sub> : 6.6 ng/mL C <sub>max</sub> : 29.5 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.9 C <sub>ss,avg</sub> : 20.5 ng/mL AUC <sub>336h</sub> : 6897 ng h/mL  <u>Risperidone plus 9-hydroxyrisperidone:</u> <i>Third injection</i> C <sub>predose</sub> : 14.5 ng/mL C <sub>min</sub> : 14.5 ng/mL C <sub>max</sub> : 48.0 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.8 C <sub>min</sub> : 15.3 ng/mL C <sub>max</sub> : 27.4 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 2.0 C <sub>min</sub> : 14.8 ng/mL  <i>Fourth injection</i> C <sub>predose</sub> : 37.0 ng/mL C <sub>min</sub> : 37.0 ng/mL C <sub>max</sub> /C <sub>min</sub> ratio: 3.6 C <sub>ss,avg</sub> : 37.0 ng/mL AUC <sub>336h</sub> : 9820 ng h/mL
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<b>Nesvag et al 2006 [135]</b>	PK study	160	Mean: 38.1– 43.4	Norway – 2 months	1 week	(1) Risperdal Consta, 25 mg/2 wk  (2) Risperdal Consta, 37.5 mg/2 wk  (3) Risperdal Consta, 50 mg/2 wk	(4) Oral risperidone 2 mg/d  (5) Oral risperidone 4 mg/d  (6) Oral risperidone 6 mg/d	Liquid chromatographymass spectrometry: Plasma concentrations	<i>Oral vs depot:</i> 9-hydroxyrisperidone: Serum concentrations MD: 21.0 nmol/L  Risperidone + 9-hydroxyrisperidone: Serum concentrations MD: 16.4 nmol/L  9-hydroxyrisperidone/risperidone ratio: MD: 9.2	<i>Oral risperidone</i> <u>4 mg vs Risperdal Consta 37.5 mg:</u> 9-hydroxyrisperidone: Serum concentrations MD: 31.3 nmol/L	
									<i>Oral risperidone</i> <u>6 mg vs Risperdal Consta 50 mg:</u> 9-hydroxyrisperidone: Serum concentrations MD: 43.0 nmol/L		
									<i>Oral risperidone</i> <u>2 mg vs Risperdal Consta 25 mg:</u> 9-hydroxyrisperidone/risperidone ratio: MD: 10.2		
									Risperidone + 9-hydroxyrisperidone: Serum concentrations MD: 31.0 nmol/L		
									9-hydroxyrisperidone/risperidone ratio: MD: 10.6		
<b>Gharabawi et al 2007 [87]</b>	Prospective, open-label, single-arm, multicenter, pilot study	87	Mean: 39.8	12 sites: USA Canada	1 year	Risperidone LAI, 50 mg/4 wk	N/A	Liquid chromatographymass spectrometry: Plasma concentrations	<i>Risperidone LAI 50 mg/4 wk:</i> C <sub>min,ss</sub> : 6.21 ng/mL C <sub>max,ss</sub> : 40.4 ng/mL t <sub>max,ss</sub> : 240.2 h AUC <sub>T</sub> : 12027 ng h/mL C <sub>avg,ss</sub> : 17.5 ng/mL FI: 199% C <sub>max</sub> /C <sub>min</sub> ratio: 7.4		
<b>Eerdekkens et al 2004 [136]</b>	Multicenter, prospective, open-label study	86	40.2	—	15 weeks	(1) Risperidone LAI, 25 mg/2 wk  (2) Risperidone LAI, 50 mg/2 wk  (3) Risperidone, 75mg/2 wk	(1) Oral risperidone, 2 mg/d  (2) Oral risperidone, 4 mg/d  (3) Oral risperidone, 6 mg/d	Radioimmunoassay: Pharmacokinetic parameters	<i>Risperidone LAI 25 mg</i> C <sub>min,ss</sub> : 11.3 ng/mL C <sub>max,ss</sub> : 22.7 ng/mL t <sub>max,ss</sub> : N/A AUC <sub>T</sub> : 5303 ng h/mL C <sub>avg,ss</sub> : 15.8 ng/mL FI: 69% C <sub>max</sub> /C <sub>min</sub> ratio: 2.4	<i>Risperidone LAI 50 mg</i> C <sub>min,ss</sub> : 24.3 ng/mL C <sub>max,ss</sub> : 57.3 ng/mL t <sub>max,ss</sub> : N/A AUC <sub>T</sub> : 11,571 ng h/mL C <sub>avg,ss</sub> : 50.3 ng/mL FI: 88% C <sub>avg,ss</sub> : 34.4 ng/mL FI: 83% C <sub>max</sub> /C <sub>min</sub> ratio: 3.9	<i>Risperidone LAI 75 mg</i> C <sub>min,ss</sub> : 32.6 ng/mL C <sub>max,ss</sub> : 80.6 ng/mL t <sub>max,ss</sub> : N/A AUC <sub>T</sub> : 16,886 ng h/mL C <sub>avg,ss</sub> : 50.3 ng/mL FI: 88% C <sub>max</sub> /C <sub>min</sub> ratio: 3.9

Thyssen et al 2010 [86]	<i>Study 1:</i> Multicenter, randomized, open-label, single-dose, 2-way crossover study	Stud y 1: 170	Study I: Mean 41	—	<i>Study 1:</i>	(1) Risperidone microspheres, 25 mg in gluteal muscle  <i>Study 2:</i> 8 weeks	N/A	<i>Liquid chromatograph y-mass spectrometry:</i> Plasma concentrations	<i>Risperidone LAI 25 mg gluteal:</i> <i>Risperidone plus 9-hydroxyrisperidone:</i> C <sub>max</sub> : 22.8 ng/mL t <sub>max</sub> : 7.1–63.0 days AUC <sub>∞</sub> : 5721 ng h/mL AUC <sub>last</sub> : 7433 ng h/mL t <sub>1/2</sub> : 6.1 days	<i>Risperidone LAI 50 mg deltoid:</i> <i>Risperidone plus 9-hydroxyrisperidone:</i> C <sub>max</sub> : 37.8 ng/mL t <sub>max</sub> : 0.08–49.0 days AUC <sub>∞</sub> : 10,370 ng h/mL AUC <sub>last</sub> : 10,369 ng h/mL t <sub>1/2</sub> : 8.1 days
	<i>Study 2:</i> Multicenter, open-label, multiple-dose study	Stud y 2: 53	Study 2: Mean: 42	—	<i>Study 2:</i> Mean: 42	(3) Risperidone microspheres, 50 mg in deltoid muscle  (4) Risperidone microspheres, 50 mg in gluteal muscle			<i>Risperidone:</i> C <sub>max</sub> : 9.91 ng/mL t <sub>max</sub> : 0.08–63.0 days AUC <sub>∞</sub> : 2222 ng h/mL AUC <sub>last</sub> : 2724 ng h/mL t <sub>1/2</sub> : 3.0 days	<i>Risperidone:</i> C <sub>max</sub> : 14.3 ng/mL t <sub>max</sub> : 0.04–38.0 days AUC <sub>∞</sub> : 3560 ng h/mL AUC <sub>last</sub> : 3548 ng h/mL t <sub>1/2</sub> : 3.2 days
								<i>Risperidone LAI 37.5 mg deltoid:</i> <i>Risperidone plus 9-hydroxyrisperidone:</i> C <sub>max</sub> : 35.4 ng/mL t <sub>max</sub> : 2.0–42.0 days AUC <sub>∞</sub> : 8334 ng h/mL AUC <sub>last</sub> : 12,462 ng h/mL t <sub>1/2</sub> : 8.3 days	<i>Risperidone LAI 50 mg gluteal:</i> <i>Risperidone plus 9-hydroxyrisperidone:</i> C <sub>max</sub> : 41.1 ng/mL t <sub>max</sub> : 2.1–56.0 days AUC <sub>∞</sub> : 10,794 ng h/mL AUC <sub>last</sub> : 11,016 ng h/mL t <sub>1/2</sub> : 6.1 days	<i>Risperidone:</i> C <sub>max</sub> : 16.8 ng/mL t <sub>max</sub> : 0.04–35.1 days AUC <sub>∞</sub> : 3895 ng h/mL AUC <sub>last</sub> : 3960 ng h/mL t <sub>1/2</sub> : 2.9 days
Wilson et al 2004 [85]	PK modeling study (1 trial)	26	—	—	—	Risperidone microspheres, 50 mg	N/A	<i>Mathematical PK modeling:</i> Plasma concentrations	<i>Risperdal Consta 25 mg/2 wk:</i> C <sub>ss</sub> achieved after 6 wk of treatment	
Gomeni et al 2013 [92]	PK modeling study (1 trial)	45	Mean: 43	—	—	(1) RBP-7000, 60, 90, or 120 mg	N/A	<i>PopPK modeling:</i> Population parameter estimates	<i>RBP-7000:</i> ka <sub>1</sub> : 0.60 h <sup>-1</sup> (fixed-effect) ka <sub>1</sub> : 0.25 h <sup>-1</sup> (random-effect) ka <sub>2</sub> : 0.24 h <sup>-1</sup> (fixed-effect) ka <sub>2</sub> : 0.12 h <sup>-1</sup> (random-effect)	
Laffont et al 2014 [90]	Phase 2a, open-label, multiple-	45	Mean: 42.6	—	—	(1) RBP-7000, 60, 90, or 120 mg/4 wk	(2) Oral risperidone 2, 3, or 4 mg/d	<i>Liquid chromatograph y-mass</i>	<i>Oral risperidone:</i> ka <sub>OR</sub> : 3.64 h <sup>-1</sup> V <sub>OR</sub> : 63.8 L	<i>RBP-7000:</i> ka <sub>1</sub> : 0.0266 h <sup>-1</sup> ka <sub>2</sub> : 0.0185 h <sup>-1</sup>

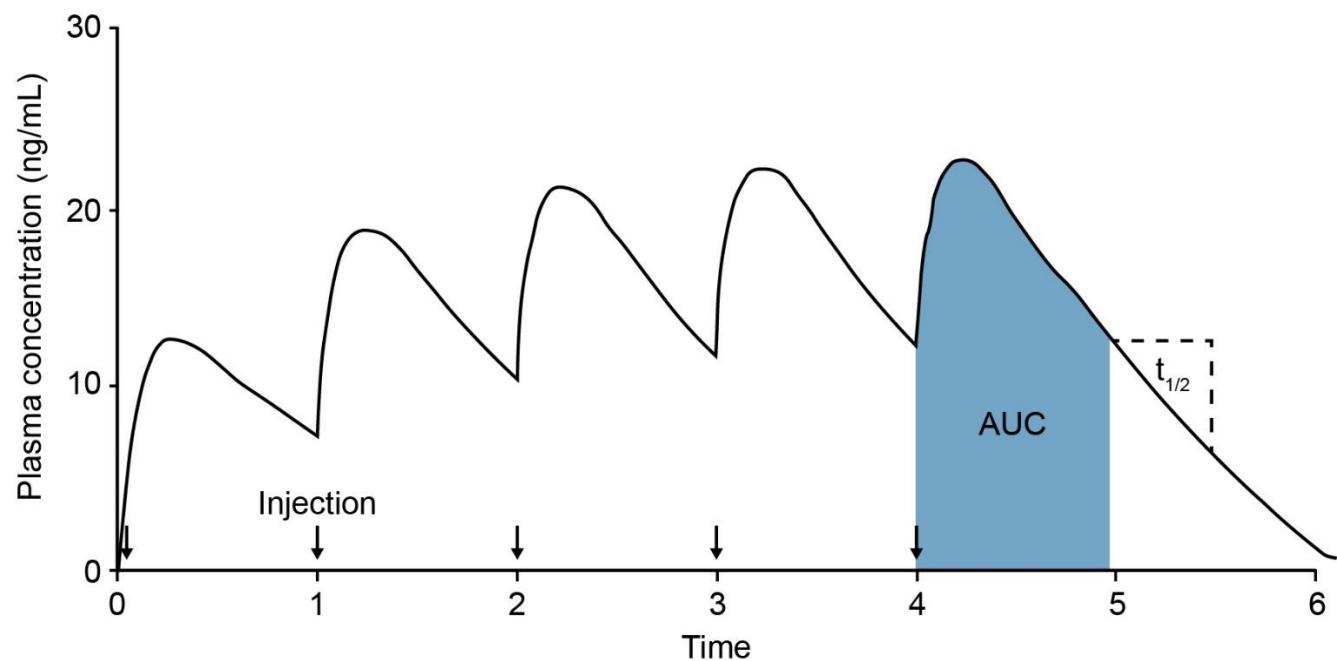
	ascending-dose study						spectrometry; <i>PopPK modeling:</i> Population parameter estimates	V: 171 L
<b>Laffont et al 2015 [91]</b>	PK modeling study (2 trials)	90 Mean: 42.8	— —	(1) RBP-7000, 60, 90, or 120 mg	N/A	<i>PopPK modeling and simulations:</i> Population parameter estimates	<u>RBP-7000:</u> $k_{a1}$ : 0.0151 h <sup>-1</sup> (fixed-effect) $C_{ss}$ achieved after 1 <sup>st</sup> injection	
<b>Ivaturi et al 2017 [116]</b>	PK modeling study (1 trial)	354 Mean: 41.2	35 sites Apr 2014– Nov 2014	(1) RBP-7000, 90 or 120 mg	(2) Placebo	<i>Liquid chromatograph y-mass spectrometry;</i> <i>PopPK modeling:</i> Population parameter estimates	<u>RBP-7000:</u> $k_{a1}$ : 0.005 h <sup>-1</sup> $k_{a2}$ : 0.016 h <sup>-1</sup> $k_{rel}$ : 0.04 V: 129.0 L	

2MPopPK 2-month population PK model, *Abs* absolute, *AL* aripiprazole lauroxil, *AL<sub>NCD</sub>* nanocrystalline milled dispersion of aripiprazole lauroxil, *AM* aripiprazole monohydrate;  $AUC_{\infty}$  area under the plasma concentration-time curve from time zero to infinite time,  $AUC_{last}$  area under the curve from time zero to the time of the last quantifiable concentration,  $AUC_T$  area under the curve over the dosing interval, *C/D* concentration/dose,  $C_{avg,ss}$  average concentration at steady state, *CL* clearance, *CL/F* apparent clearance,  $C_{max}$  maximum plasma concentration,  $C_{max}/C_{min}$  peak to trough ratio,  $C_{min}$  minimum concentration, *ER* extended release, *F* absolute bioavailability, *f/f* fraction of the dose released in the first release process, *FI* fluctuation index, *HPLC* high performance liquid chromatography, *IM* intramuscular, *IR* immediate release,  $k_{a1}$  first-order absorption rate constant,  $k_{a1,max}$  maximum absorption rate for the slow absorption process,  $k_{a3,max}$  maximum absorption rate for the rapid absorption process,  $k_{a2}$  rate constant for the slow absorption,  $k_{aOR}$  rate constant for the rate of risperidone, *kel* elimination rate constant, *LAI* long-acting injectable, *LC-MS/MS* liquid chromatography-mass spectrometry/mass spectrometry, *MD* mean difference of serum concentrations, *N/A* not applicable, *P-gp*, p-glycoprotein, *PK* pharmacokinetics, *popPK* population pharmacokinetics, *PP* paliperidone palmitate, *PP1M* paliperidone palmitate once-monthly, *PP3M* paliperidone palmitate every-3-months,  $qXw$  every *X* weeks, *SC* subcutaneous, *ss* shape of the first release process, *ssi* shape of the second release process, *t<sub>1/2</sub>* half-life, *td* time to absorb 63.2% of dose released in the first process, *tdI* time to absorb 63.2% of dose released in the second process, *TDM* therapeutic drug monitoring, *t<sub>max</sub>* time to reach observed maximum plasma, *V* volume of distribution, *VOR* volume of distribution of the central compartment,  $V_{ss}$  volume of distribution at steady state.

<sup>a</sup>3 citations (Ehret et al. 2018, [41] Jann et al. 1985, [42] and Vermeir et al. 2008 [43]) were included in the original literature analysis though they did not meet inclusion criteria, as described in Methods. Two articles are reviews and one article describes oral paliperidone; therefore, these articles are not summarized in this table.



**Supplemental Figure 1. Pharmacokinetics Concepts Within a Plasma Concentration-time Curve**



AUC = area under the curve;  $t_{1/2}$  = elimination half-life.

**Supplemental Figure 2. Mean plasma levels of risperidone plus 9-hydroxyrisperidone (“Active Moiety”) after a single dose of 25 mg of long-acting risperidone in 14 patients with schizophrenia [136]**

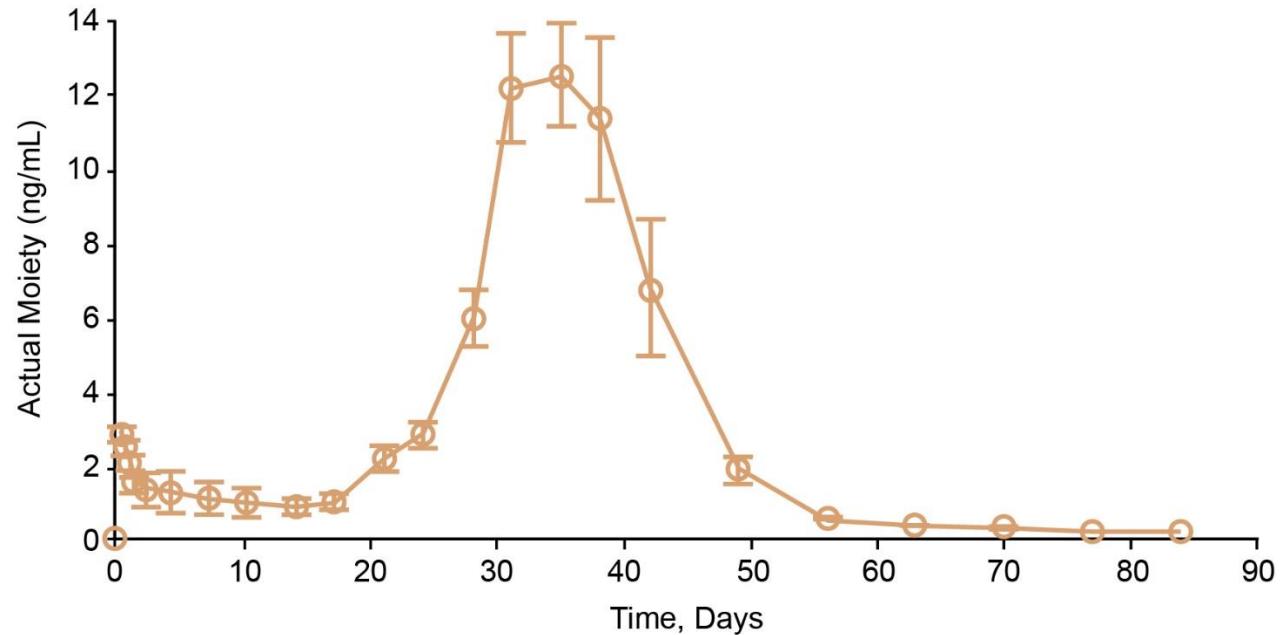


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